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HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

99D-2873 '99 NOV 30 P1:03

November 30, 1999

Dockets Management Branch
HFA-3 05
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 99D-28 73

Dear Madam or Sir:

The Health Industry Manufacturers Association (HIMA) is pleased to provide comments on the Food and Drug Administration's (FDA) *"Draft Guidance on Evidence Models for the Least Burdensome Means to Market."* HIMA is a Washington, D.C.-based trade association and the largest medical technology association in the world. HIMA represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. HIMA's members manufacture nearly 90 percent of the $62 billion of health care technology products purchased annually in the United States, and more than 50 percent of the $147 billion purchased annually around the world.

As a result of FDA's January 1999 meeting on "least burdensome," HIMA initiated the formation of an industry task force consisting of representatives from several medical device organizations. This task force developed the enclosed comments on FDA's draft guidance. HIMA fully endorses the industry task force comments.

HIMA appreciates the opportunity to submit the enclosed comments and looks forward to meeting with the agency as part of the Industry Least Burdensome Task Force to discuss the guidance document.

Sincerely,

Janet Trunzo

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Associate Vice President
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jt:ts

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HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

JAMES S. BENSON
EXECUTIVE VICE PRESIDENT, TECHNOLOGY AND REGULATORY AFFAIRS

November 24, 1999

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-2873

Dear Sir or Madam:

The Least Burdensome Task Force (the Task Force), a coalition of members from the medical device industry, is pleased to provide the following comments on the Food and Drug Administration's (FDA) *"Draft Guidance on Evidence Models for the Least Burdensome Means to Market."* The Task Force is comprised of representatives from the following organizations: Health Industry Manufacturers Association (HIMA), Medical Device Manufacturers Association (MDMA), National Electronic Manufacturers Association (NEMA), Association of Medical Diagnostics Manufacturers (AMDM), Joint Council of Immunohistochemical Stain Manufacturers (JCIM), Massachusetts Medical Device Industry Council (MassMEDIC), Medical Alley, Indiana Medical Device Manufacturers Council (IMDMC), and the Cook Group.

The "Least Burdensome" provision, Section 205 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), is a major provision of FDAMA designed to reduce the burden and time required to bring new safe and effective medical devices to patients in the United States. The intent of FDAMA is to foster collaboration between the Center for Devices and Radiological Health (CDRH) and device sponsors to determine the least burdensome means of product approval and market introduction. Industry's commitment is reflected in our participation in FDA's "least burdensome" stakeholders meeting and in our development of the early proposal for least burdensome determinations. FDA's inclusion of the industry proposal is recognition of that commitment. The Task Force also welcomes the FDA's draft guidance as an important step forward and acknowledges the agency effort that this represents. We strongly agree that the guidance needs to take a process approach to the determination of least burdensome requirements. This is critical to develop common understanding between industry and CDRH as well as consistency in implementation across Office of Device Evaluation (ODE) divisions. Both the FDA and Task Force proposals are process-based albeit with different

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approaches. The Task Force also agrees with the "General Principles" outlined in the draft guidance. It is critical that they be translated directly into the least burdensome determination process. Finally, we agree with FDA that its draft guidance is a first step in that it focuses only on clinical data needs and specifically excludes in vitro diagnostics (IVDs). Direct collaboration between CDRH and industry is needed to develop a comprehensive "least burdensome" guidance.

The Task Force believes that a comprehensive "least burdensome" guidance would benefit greatly from a joint effort and thus recommends that CDRH form a "least burdensome" working group, consisting of industry, CDRH and other appropriate participants to revise the published draft guidance document. In the past, there have been many instances of industry/agency collaboration and dialogue that have resulted in strong programs such as the Product Development Protocol reengineering initiative, and the PMA Supplement and 5 1 O(k) modifications guidance documents. As the Task Force noted in its letter dated November 15, 1999 to Dr. David Feigal, the Task Force is looking forward to the meeting with the agency to discuss these comments and to explore ways in which industry and the agency can work together to revise the guidance document.

In recent testimony before the Senate Committee on Health, Education, Labor, and Pensions (HELP) on October 21, 1999, Pamela Baiiey, president of HIMA, stressed the need to restore industry/agency discussion prior to issuing guidance documents or shaping programs'. The need for industrylagency interaction in the area of "least burdensome" is of the utmost importance. We believe that the lack of industry/agency dialogue resulted in FDA's misunderstanding and mischaracterization of the least burdensome proposal submitted by the Task Force. Contrary to being the arduous process described by FDA, the industry proposal closely tracks Congress's intent in enacting the FDAMA provisions requiring consideration of the "least burdensome" means of supporting device approvals or clearances. Through comments and collaboration with FDA, we hope to avoid misunderstandings and constructively contribute to making Congress's FDAMA approach work.

The Task Force welcomes the opportunity to provide comments on the draft guidance. Our comments are directed at identifying the key issues for further discussion and resolution and we look forward to collaborating with FDA to develop comprehensive guidance.

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[1] Testimony of Pamela G. Bailey. Health Industry Manufacturers Association. Hearing on Implementation of the Food and Drug Administration Modernization Act of 1997 before the Senate Committee on Health, Labor, Education and Pensions, October 21, 1999.

Definition of Least burdensome and a Process for Implementation

To achieve the intent of FDAMA in the implementation of the least burdensome provision, the Task Force recommends the need for both a functional definition and a process for least burdensome. We propose to define least burdensome as:

> Determining the most appropriate level of (1) valid scientific evidence for PMA devices to determine reasonable assurance of device effectiveness or (2) information necessary to demonstrate substantial equivalence for 5 10(k) devices. The process for determining this most appropriate level should confine submission requirements to essential issues to support approvals or clearances, eliminate inappropriate and unnecessary testing and FDA reviews, and provide an opportunity for prompt resolution of scientific differences between FDA and device sponsors thereby ensuring the development and market approval and clearance of new, beneficial devices without delays attributable to over-regulation.

Further, we believe that the least burdensome concept is best implemented by a process that will produce understanding between FDA and industry on the level of appropriate data needed to establish a reasonable assurance of safety and effectiveness or substantial equivalence. Because data requirements are specific to each type of device, the process must include an effective and objective methodology for determining what data are essential, for eliminating nonessential data requirements and for promptly resolving disputes. In other words, obtaining a least burdensome result for a specific device process is best achieved through a well-defined and interactive process between FDA reviewers and device manufacturers.

To be effective, the process must include steps to:

- identify the issues or questions related to safety and effectiveness or substantial equivalence,
- discriminate between essential and nonessential issues on the basis of scientifically sound rationale,
- eliminate nonessential data requirements,
- establish practical methods for determining essential data, and
- resolve disputes between FDA and industry regarding a least burdensome determination through a fair, equitable, and efficient process.

For PMAs, least burdensome is defined primarily by clinical data which are valid scientific evidence within the meaning of 21 CFR 860.7(c)(2). While this regulation refers to clinical

trials, for PMA devices, data from laboratory (chemical, electrical, mechanical) or pre-clinical animal studies are also implicitly within the scope of the least burdensome process because such data serve to limit the clinical testing requirement.

Requirements for valid scientific evidence should be confined to answering only those questions that are pertinent and essential. Focused studies are more likely to yield definitive results. In many cases, studies are expanded beyond the essential issues with the misconception that they are more comprehensive when, in fact, they are less focused and result is less definitive data. For example, a well-defined laboratory or animal study may substantially answer an effectiveness issue, thus limiting the scope and kind of clinical study that would be necessary to demonstrate device effectiveness, or completely eliminating the need for a clinical trial.

The process should recognize the importance of eliminating non-essential efforts. The unnecessary consumption of resources and time for non-essential testing detracts from and diverts resources from more productive efforts and often leads to uncertainty and delays in the' review process. Therefore, it is important to acknowledge that some tests are nonessential. Nonessential tests may include laboratory, animal or clinical testing involving outdated methods, previously-answered questions, curiosity questions, testing requirements and requests due to reviewer inexperience or lack of specific knowledge, impractical methods and methods beyond those required to obtain or adequately analyze the data.

The most likely process to succeed is one in which data requirements are commonly agreed to by industry and FDA and are listed as such. When industry and FDA disagree about data requirements, there must be a formal process to require both FDA and industry to document scientifically sound justifications and counter-arguments. Documentation should be sufficient to allow an independent party to make judgments based on the scientific merits. Further, all existing product-specific guidance documents should be reviewed by FDA to determine whether they comply with the least burdensome concept. Additionally, future FDA guidance documents including data requirements should be developed cooperatively and with least burdensome concepts in mind. By establishing mutually agreed upon data requirements, the variability created by the range of industry and reviewer knowledge and experience is minimized.

The development of a process for establishing the least burdensome methods has several advantages while not compromising the scientific rigor of premarket testing. It focuses testing and review efforts to address essential issues and minimizes workload for all parties. Industry and FDA resources can be better directed for a more controlled review process, with the benefits of improving global competitiveness and reducing the delays in patients' access to new beneficial medical technology.

Scope of guidance

The scope of the industry proposal covers all devices, consistent with the least burdensome provisions of FDAMA. The proposal also covers all types of devices regulated through the 5 1 O(k) and PMA processes, including IVD devices. FDA appears to understand the Food Drug and Cosmetic Act (the Act), yet failed to draft its guidance in parallel with the scope of the law. Although FDA states on page 2 in the section entitled "Scope of this guidance," the intent to "establish a general approach for applying least burdensome provisions that will be applicable to any device application," CDRH describes the guidance as limited to clinical data and excludes IVDs because of purportedly "unique clinical data needs associated with establishing IVD performance." The Task Force does not accept the argument for the IVD exclusion. There is uniqueness in other types of devices, and therefore, IVDs should not be singled out, particularly if the broad concepts of least burdensome are adopted

FDAMA's "least burdensome" provision applies to all devices, does not distinguish between types of devices, and is not limited to PMAs or to 5 1 O(k) submissions requiring clinical data. We believe that this very limited scope greatly detracts from the value of the guidance document to FDA reviewers and industry and fails to meet the spirit of FDAMA's provisions for "least burdensome." On page 5, first paragraph, CDRH acknowledges that for 5 1 O(k) submissions, "new clinical data are not required in most of these circumstances." As such the number of devices/manufacturers having access to "least burdensome" will be quite small. Per the ODE Annual Report, Fiscal Year 1998, (55) PMA submissions were received compared to (4,623) 5 1 O(k) submissions, with only approximately 10% of 5 1 O(k) submissions requiring clinical data.

We recommend that, before implementation, the draft guidance be revised to include all types and classes of products, including IVDs, as well as consider "least burdensome" for all types of data. By increasing the scope in this way, *all* device submissions would have access to "least burdensome." Most 5 1 O(k) submission reviews would benefit if 5 1 O(k) submission information were limited to that information necessary to a substantial equivalence determination. IVD submissions would be considered under the same policies as other medical device submissions. To address the agency's concern that a broader scope would be unwieldy, we believe that developing a decision tree with textual guidance like that used to develop the guidance "When to Submit a 5 1 O(k)" would be an effective means to make the process work. We are prepared to assist CDRH as part of an industry/agency least burdensome task force in achieving this goal.

Are Randomized Controlled Trials Least Burdensome?

In FDA's model, the second consideration for determining least burdensome clearly reflects the agency's bias toward Randomized Controlled Trials (RCTs). However, the suggestion that RCTs

are least burdensome warrants further scrutiny. FDA states, "stakeholders have tended to focus concerns regarding the least burdensome decision related to the need for an RCT because they have assumed that an RCT will be more costly in terms of time and money." Industry's concern is stated correctly and the industry proposal included clear examples where RCTs are indeed more burdensome. FDA maintains that RCTs are not always more costly in time and money but offered no data or examples in support of this view.

Clearly there are some devices for which RCTs are least burdensome. But the Task Force believes that these represent only a small percentage of devices that require clinical data to support safety and effectiveness or substantial equivalence.

RCTs are the paradigm for determining drug safety and efficacy. This is appropriate because each molecular entity is a new drug, the interaction of an active ingredient with different inactive ingredients may vary drug effectiveness, and drugs generally act systemically. Their effects – positive and negative – are often subtle.

Fundamental differences between drugs and devices limit the need for RCTs for device studies and therefore make the requirement for RCTs overly burdensome. Consider:

- Device action is generally more localized and specific and its clinical effects more readily apparent.

- One of the rationales for RCTs in drugs is to eliminate the placebo effect. For many devices, particularly implants and others involving surgical procedures, there is little or no placebo effect.

- Devices evolve over time through a series of incremental improvements. This means that historical data very often exist which provide a valid control.

- Device evolution also means that very often the issues of safety and effectiveness or substantial equivalence are focused on incremental features rather than the device as a whole, thus limiting the need for clinical data when bench data is fully adequate to address the change.

FDA indicates that RCTs are the easiest for FDA to review. This is most evident in the agency's assessment of the industry least burdensome model. We strongly disagree with that assessment. For the majority of devices requiring clinical data, RCTs are not least burdensome. Guidance structured by the industry proposal provides a simple, direct process for FDA and the device

sponsor to jointly identify the most appropriate level of valid scientific evidence and the least burdensome approach. Once this is done, FDA review should be straightforward.

Comparison of FDA's Least Burdensome Model with Industry's Least Burdensome Model

We believe that the industry model is consistent with congressional intent for the least burdensome provision because it is inclusive of all types of devices, e.g., IVDs, and it applies to both PMA and 5 1 O(k) submissions. Additionally, the industry model defines a process that begins with the base of the hierarchy of valid scientific evidence while the FDA model begins its approach with RCTs (the very top of the hierarchy) and does not consider the other types of valid scientific evidence on the hierarchy. The Task Force strongly believes that its approach is more appropriate for the following reasons.

- The FDA model starts with the premise that the RCT is best and is least burdensome. This directly conflicts with congressional intent. Congress enacted the least burdensome provision because of concern that FDA's long approval and clearance times were unnecessarily and unreasonably delaying the availability of new improved medical devices. Part of that is directly attributable to CDRH's efforts following the Temple Report to implement a drug model for device evaluation with its attendant emphasis on RCTs. Because of the differences in the nature of development, mode of action, etc, the need for RCTs to evaluate safety and effectiveness is far less for devices than for drugs. Unnecessary demands for randomized controlled trials add excessive burden to the product life cycle.

- The FDA model also requires proof by the device sponsor that any alternative is better and less burdensome. No matter how good the process is for decision making, this model includes bias that will inevitably lead to more RCTs than necessary and more rather than less burden. We believe the industry model will more likely lead to the determination of the appropriate level of scientific evidence necessary to support market approval.

- FDA's perspective of least burdensome is limited to its own role-i.e., in the review of device submission data. We believe congressional intent in mandating least burdensome was to minimize the burden on all parties (FDA, patients, clinical investigators and industry) and speed the time to market which also means reducing the duration of development and clinical cycle times. FDA's perspective will, without question, add time, cost, and burden to the investigation of devices. We also reject the notion that RCTs are themselves less burdensome for FDA to review. The appropriate level of scientific evidence to the device in question should require the least time and effort for FDA review and this will be achieved more readily through the industry model.

- The industry model better addresses the spectrum of device clinical trials. The role for RCTs may be more appropriate to new breakthrough devices and therapies (i.e. those that require a first PMA), although even this statement is a generalization that is limited by numerous examples. In fact, breakthrough devices represent a minority of device clinical trials. For most devices subject to marketing via 5 1 O(k) and for many second and third generation PMA devices, there are specific focused issues that require clinical data to support market approval. For these devices the appropriate level of valid scientific evidence is below RCTs on the valid scientific evidence hierarchy.

Finally, we believe that FDA has misinterpreted the industry model by implying that each level of the hierarchy represents a submission of data that must be reviewed by FDA, thereby adding delays. We believe that the industry model, like FDA's, is a process model. The industry model uses examples to help determine the appropriate level. Although the FDA model uses a series of questions, it does not provide a well-defined structure that would predictably allow one to reach a correct least burdensome decision. We believe that a flowchart of questions and examples could be developed to further strengthen the industry model. We propose that this be done in collaboration with FDA. As a final note, FDA's criticism of the purportedly arduousness of the industry approach, if applied to the agency's approach, would lead to the same criticism.

Consideration of Least Burdensome in Determination Meetings

Section 205 of FDAMA includes both the least burdensome provision and the provision for an early determination meeting with FDA. The purpose of the determination meeting is for FDA to specify the type of valid scientific evidence necessary to support PMA approval for the device in question. Clearly congressional intent is that this determination must be made in the context of the least burdensome requirement. To date, FDA has gone out of its way to discourage determination meetings by implying none too subtly that determinations from such meetings would not be least burdensome. For example, shortly after FDAMA passage, Dr. Bruce Burlington stated that FDA's default position would be to require RCTs. This attitude has not changed as reflected by Dr. Susan Alpert's comments at the most recent RAPS conference as quoted in the October 11, 1999 issue of the Gray Sheet. Dr. Alpert recommended sponsors pursue non-binding meetings in lieu of a binding determination meeting saying, "you can have [a determination meeting], but we think that gives [FDA] an awful lot of latitude to decide the terms of the binding agreement." If FDA was committed to implementing the least burdensome approach, the agency would use determination meetings as a way of putting "meat on the bones" of the least burdensome concept and, therefore encourage and not discourage such meetings. Moreover, the industry "bottom up" model provides a better, more harmonious means of

consulting in a determination meeting in comparison to a meeting focused on overcoming FDA's RCT presumption.

Least Burdensome: 5 1 O(k) vs. PMA Determinations

The draft guidance clearly applies to products cleared by 5 1 O(k)s and approved by PMAs where clinical data are required. The FDA's proposal fails to consider the bulk of 5 1 O(k)s that do not require clinical data to resolve technological differences. Also, we believe the draft guidance fails to consider another aspect of 5 1 O(k)s and PMAs that should involve a least burdensome consideration. Specifically, FDA's guidance should consider whether changes in technology, indications, etc., associated with a device initially cleared by 5 1 O(k) should be marketed via a 5 1 O(k) or PMA. The FDA's presumptive position should be for the agency to clear these products by 5 1 O(k). Data requirements, FDA and sponsor resource requirements, and regulatory cycle times increase substantially when a device goes from 5 1 O(k) to PMA. This result would not be a least burdensome undertaking. A good example of this is digital mammography systems. Current technology is marketed via 5 1 O(k) but FDA appears ready to require a PMA for digital mammography. In the October 4, 1999 issues of the Gray Sheet, Dr. Feigal is quoted as saying "although it sounds paradoxical, a PMA is something that may be less burdensome than a 5 1 O(k) [for digital mammography] (emphasis added)." If predicate technology can be adequately regulated via 5 1 O(k), there is little or no additional public health benefit that would justify the additional burden of the PMA process.

When considering whether or not to place a device onto a PMA track, FDA should aggressively use risk-based classification under section 513(f)(2) of the Act to avoid over-regulation, consistent with FDAMA's least burdensome philosophy. By assessing risk before requiring a PMA, FDA can avoid large burdens to itself and industry when a device could be regulated successfully as a class II or I device. This approach is especially sensible when FDA has extensive experience with devices that are PMA candidates because of changes in indications of use. By virtue of its experience, FDA can evaluate such a device's likelihood for harm in the context of a new indication. Depending on the significance of the new indication, and FDA's experience with a device, a reasonable risk-based determination can be made, thus providing FDA with the opportunity to avoid unnecessary PMAs.

Premarket Notification

FDA's proposed guidance fails to address the breadth and scope of the statute in the development of least burdensome requirements for all devices and particularly those subject to 5 1 O(k) clearance. An effective least burdensome guidance document must also address other issues that are not exclusive to premarket submissions for which clinical data are required. As acknowledged in the FDA draft guidance, very few 5 1 O(k) submissions will require clinical data

to demonstrate substantial equivalence. The need, therefore, exists to develop least burdensome criteria that do not focus primarily on clinical data requirements.

The need for non-clinical data in a 5 1 O(k) will vary depending on the type of device and experience with its use. For many products non-clinical data (biocompatibility, electromagnetic compatibility, internal results from design verification and validation) are sufficient to satisfy substantial equivalence determination and support the clearance of the device. For 5 1 O(k) products, it should be a very rare circumstance when manufacturing data and other information more appropriate for a PMA submission are required in a 5 1 O(k). Unless, for example, there are issues unique to the manufacture of a particular device subject to 5 1 O(k) requirements, these types of issues should be left to FDA field inspection and should not be part of ODE review.

For those very few 5 1 O(k) submissions that do need clinical data to demonstrate substantial equivalence, it is important to note that the type of data and the clinical endpoints must be commensurate with 5 1 O(k) substantial equivalence requirements. For example, the type of data or endpoints needed as the basis of a substantial equivalence determination would not address clinical utility. We recommend that a revised guidance clearly state the difference in type of clinical data and endpoints needed for a 5 1 O(k) submission as compared to a PMA submission

Guidance needs to consider device risk in determining what data – clinical or preclinical-are needed to support a substantial equivalence decision. 5 1 O(k) devices inherently pose a lesser risk than PMA devices. The gradation in risk in the 5 1 O(k) device population also needs to be addressed. The Task Force recommends that FDA and industry work together to develop comprehensive guidance rather than one with such limited applicability.

Premarket Approval and 510(k)s with clinicals

Role of non-clinical data in clinical decisions and requirements

The language of the Act as modified under FDAMA indicates that clinical studies shall be required for PMA approval only when "necessary", i.e., when there is not other sufficient valid scientific evidence to support approval. Further, the extent of data required for approval must be considered in light of possible postmarket controls. This clearly demonstrates congressional intent that clinical studies be required only after due consideration of all reasonable alternatives, not as the starting point in the early discussions between FDA and the device sponsor including Determination Meetings provided under FDAMA. Thus, we believe that non-clinical data must be considered first when evaluating the least burdensome means of demonstrating the safety and effectiveness of a Class III device. This approach is not only consistent with the language of FDAMA, but also consistent with the provisions of the Quality System (QS) Regulation Design Controls.

Question 1 in the FDA Draft Guidance states "Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population? (emphasis added)." Valid scientific evidence is generally construed to reflect clinical data. The context of this question needs to consider the preclinical testing for the device at issue as well as any prior clinical testing in determining whether there is reasonable assurance that this device is safe and effective or substantially equivalent without additional clinical data.

While the FDA is correct in stating that industry is concerned with FDA's interpretation of least burdensome requirements as they relate to clinical trials, the FDA has misinterpreted industry's concern. The industry is concerned not just with what type of clinical data are of least burden, but also with the burden imposed through the collection of clinical data when it is not really needed.

Break-through technology

Industry recognizes that the revolutionary device by its very nature will raise new technological questions. Thus, these are the devices where the probability is greatest that a clinical study may be appropriate. However, even breakthrough devices may not need or be suitable for a RCT.

FDA guidance needs to incorporate risk analysis consideration into the least burdensome determination process. The QS Regulation, combined with the growing acceptance of international quality system standards in the medical industry, has focused attention on risk analysis as a central tenet of design control. Under design control (21 CFR 820.30), the manufacturer is tasked with identifying the potential hazards associated with the new device. Following risk analysis, the type of design validation required is to be determined based on the identified issues. Thus, the scientific questions associated with potential clinical hazards should be well defined via risk analysis prior to defining the design validation program, including any required clinical studies. We believe that the determination of the type of valid scientific evidence necessary to demonstrate effectiveness in a PMA must be linked to these design validation questions in order to be considered least burdensome. Further, the burden on the sponsor, clinicians and patient populations to generate the data, not just the ease of the subsequent review process, must be considered in determining the most appropriate study design.

Early dialogue/consultation with FDA

In order to reach an optimal determination of the least burdensome, appropriate means of demonstrating safety and effectiveness, the manufacturer must be able to meet with representatives of the review division to assure a common understanding of the potential risks and benefits of the new technology. The industry is best suited to inform FDA about these break-

through technologies. Early discussions with the FDA using a comprehensive process model for a least burdensome determination can identify the necessary burden for establishing safety and effectiveness. FDA's assumption that multiple submissions would be required in the industry model as used represents a fundamental misunderstanding that can be resolved in the development of a comprehensive model. Early collaboration is essential for the mutual education and exchange of ideas that must occur for break-through technologies to be brought to market in an expeditious manner.

Safety & Effectiveness

Following the initial dialogue, an open consultation between FDA and sponsors should continue to determine the most appropriate clinical means of addressing those questions raised by the risk analysis that cannot be addressed through non-clinical means. These discussions should continue under the auspices of the formal early collaboration meetings anticipated by the FDAMA provisions for determination and agreement meetings as the mechanisms for identifying the least burdensome means of establishing safety and effectiveness. Further, this consultation can and should be based on a comprehensive process model incorporating the hierarchical principles outlined in the industry proposal.

The examples in FDA's draft guidance suggest that innovators must pave the way with RCTs before less burdensome approaches to establishment of safety and effectiveness will be considered by FDA. This argument is flawed for several reasons. First, such trials are not always appropriate. There may be ethical considerations making randomization improper or logistical considerations impeding effective masking of the trial. The examples provided with the industry proposal include examples where RCTs were inappropriate. Second, the automatic assumption that RCTs should be considered first, as presented in the draft guidance, is a potential disincentive to innovation, as such trials are clearly not viewed as least burdensome by the device industry. The open consultation contemplated by FDAMA requires equal consideration to alternative forms of valid scientific evidence.

Pre-market vs. post-market studies

Whenever possible, postmarket controls must be considered as an alternative or adjunct to preapproval trials. This is particularly important in the case of break-through devices where a satisfactory diagnostic or therapeutic alternative is not available or where a new device offers significant safety and effectiveness advantages. One can always ask that additional data be gathered to address a "suspicion" or long-term concern about a particular device. The concept of least burdensome requirements is one in which such concerns must be deemed insufficient to delay approval. If the patient group being treated by the device is at significant risk from the lack of the treatment, the FDA should consider the use of post-market studies in reducing the

pre-market burden. FDA supports the use of postmarket studies as a means to reduce premarket testing and the least burdensome process model is the ideal way to incorporate its consideration. To date there has been little evidence that FDA has considered the pre- and postmarket trade off in early discussions of market approval and clearance requirements.

Device evolution and least burdensome

Clinical requirements for device changes

Breakthrough devices represent only a fraction of the agency's PMA workload. The remainder is comprised of devices reasonably known to the FDA and the medical community. These include many original PMAs, for example "me-too" or pre-amendments devices for which ample historical data exist to address most, if not all, of the design validation issues. Where clinical data are needed, clinical studies can and should be focused on specific issues and differences from previous devices.

The remainder of the PMA workload consists of PMA supplements. Design control can again play a role in determining if there is a need for clinical data for device modifications requiring PMA supplements. The QS Regulation requires the manufacturer to determine the potential impact of any proposed device modification via the risk analysis. Following risk analysis, the type and extent of design verification and/or validation required is based on the potential hazards associated with the device change.

Thus for evolutionary devices, the type of clinical data, if any, can easily be determined through a comprehensive least burdensome process model as described above. It may well be that design verification or simulated use studies are sufficient to address the scientific questions raised via the risk analysis. Alternatively, the scientific literature may provide ample evidence that the modification (e.g., a materials change) will not impact safety or effectiveness. In cases where design validation requires clinical testing, an open-label study to confirm that any potential new risks remain within acceptable risk:benefit ratios may suffice. Even if a well-controlled study was deemed necessary for the parent device, a small, confirmatory study with historical controls may be sufficient to validate the continued safety and effectiveness of the device following modification.

Use of literature

As discussed above, scientific literature can and should be appropriately used to reduce the premarket burden on device manufacturers. Where well-documented case histories and reports of significant human experience are relevant to the product modification, these types of valid scientific evidence must be considered prior to requiring new clinical data. The Task Force

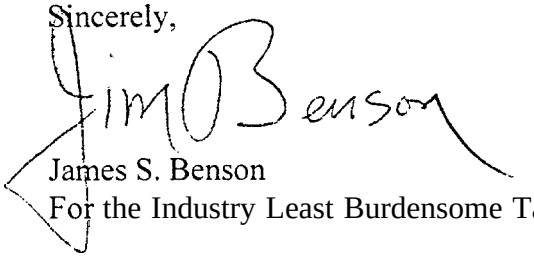
believes that a comprehensive model for least burdensome determinations incorporating risk analysis can identify conditions where the use of literature is acceptable.

Appropriate controls for clinical studies

FDA's draft guidance sets RCTs as the initial point of consideration for any clinical trial design. Given the spectrum of devices and clinical issues, this one-size-fits-all approach is inappropriate and inherently burdensome. Industry is required to prove that something less is more appropriate which FDA reviewers are unlikely to accept. The industry proposal based on the tiered hierarchy of valid scientific evidence presents a more realistic and meaningful approach to address the spectrum of medical devices. FDA concerns, we believe, represent misunderstandings that can be addressed by providing more detail in the process model and we are prepared to work with FDA to achieve this.

In conclusion, we would like to reiterate the need for an interactive process in revising the draft guidance document and the willingness of the Task Force to participate in a "least burdensome" working group, consisting of industry, CDRH, and other appropriate participants to revise the guidance. Industry's Least Burdensome Task Force is very committed to working with the agency to accomplish the revision and would like to accept FDA's offer to meet after the conclusion of the official comment period. Again, we appreciate the opportunity to provide these comments.

Sincerely,



James S. Benson
For the Industry Least Burdensome Task Force